

REMARKS**Amendments to the Specification**

The specification at page 18 has been amended to correct grammatical errors and to correct the name of the PMO compound. Specifically, the word “phosphothioate” has been replaced with the word “phosphorodiamidate”. The correct name associated with the term “PMO” was well known in the art at the time of filing. Accordingly, no new matter has been added by way of these amendments.

Amendments to the Claims

Claims 1-25 are currently pending. Claims 1-3, 6, 8, 9-11 have been amended. Claims 12 and 16-19 have been canceled without prejudice or disclaimer. Claims 4-5, 7, 13-15, and 20-25 have been withdrawn as drawn to a non-elected invention.

Claim 1 has been amended to recite that the first assay system is capable of detecting PRKC expression and to add several steps, including measuring the expression of PRKC in the presence or absence of the test agent and identifying a candidate beta catenin modulating agent by detecting a change in the expression or activity of PRKC in the presence or absence of the test agent, as well as reciting that the method comprises a second assay system capable of detecting a change in the beta catenin pathway comprising cultured cells expressing PRKC, contacting the second assay system with the test agent, and determining a change in the beta catenin pathway in the second assay system. Support for the amendments can be found throughout the specification and in original claim 16.

Claims 1-3, 6, 8, 9-11 have been amended to correct grammatical errors. In addition, claims 2 and 8 have been amended to clarify that the assay system is the first assay system. Claim 6 has been amended to clarify that the assay system is the second assay system. Support for the amendments can be found throughout the specification, particularly at, for example, pages 20-29 and 30-33.

Claim 8 has been amended to recite that the nucleic acid modulator is a phosphorodiamidate morpholino oligomer (PMO). Support for the amendment can be found in the specification at page 18.

Claim 11 has been amended to recite that the cultured cells in the second assay system additionally have defective beta catenin function. Support for the amendment can be found in the specification at, for example, page 33.

The claim amendments are made solely in an effort to advance prosecution and are made without prejudice, without intent to acquiesce in any rejection of record, and without intent to abandon any previously claimed subject matter. No new matter has been added by way of these amendments.

Rejection of Claims Under 35 U.S.C. § 112, second paragraph

Claims 5, 10, and 16 were rejected under 35 U.S.C. 112, second paragraph. Claim 16 has been canceled, rendering the rejection moot as to that claim.

Claim 5 was rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite because it recites “the assay” without proper antecedent basis. Although claim 5 is not currently under examination, it has been amended to recite “the screening assay”, thereby obviating the rejection. Applicants respectfully request withdrawal of the rejection.

Claim 10 was rejected under 35 U.S.C. 112, second paragraph, as being indefinite because it is allegedly unclear what is intended by “PMO”. Claim 10 has been amended to clarify that “PMO” refers to “phosphorodiamidate morpholino oligomer”. Applicants respectfully request withdrawal of the rejection.

Rejection of Claims Under 35 U.S.C. § 102

Claims 1, 2, 6, 8, and 9 were rejected under 35 U.S.C. 102(b) as allegedly anticipated by Murray et al (J. Biol. Chem., 268:15847-15853 (1993)). Applicants respectfully traverse the rejections.

The Office alleged that Murray et al. disclose a proliferation based assay wherein cells that express PKC α , β , and ζ were treated with antisense against PKC β . The Office stated that “the active method steps of the rejected claims provide absolutely no nexus between beta catenin, PRKC, and the candidate agents, such that these claims are anticipated by any prior art method in which an antisense oligonucleotide is added to cells in a proliferation assay, wherein the cells comprises PKC nucleic acids.” Office Action, page 5.

Under 35 U.S.C. § 102, a claim is anticipated only if each and every element as set forth in the claim is found in a single art reference. *Verdegaal Bros. v. Union Oil Co.*, 814 F.2d 628, 631, 2 USPQ2d 1051, 10533 (Fed. Cir. 1987); *Structural Rubber Products Co. v. Park Rubber Co.*, 749 F.2d 707, 716 (Fed. Cir. 1984) (All elements of the claimed invention must be contained in a single prior art disclosure and must be arranged in the prior art disclosure as in the claimed invention); M.P.E.P § 2131. The identical invention must be described or shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989); *Chester v. Miller*, 15 USPQ2d 1333 (Fed. Cir.1990); M.P.E.P. § 2131.

Applicants submit that Murray et al. do not teach all of the elements of the presently claimed methods. The claims, as amended, recite a method of identifying a candidate beta catenin pathway modulating agent comprising (a) providing a first assay system capable of detecting Protein Kinase C (PRKC) expression comprising a PRKC nucleic acid; (b) contacting the assay system of step (a) with a test agent; (c) measuring the expression of PRKC in the presence or absence of the test agent; (d) identifying a candidate beta catenin modulating agent by detecting a change in the expression or activity of PRKC in the presence of the test agent compared with no test agent; (e) providing a second assay system capable of detecting a change in the beta catenin pathway comprising cultured cells expressing PRKC; (f) contacting the assay

system of step (e) with the candidate test agent of step (b); (g) measuring the beta catenin pathway in the presence or absence of the test agent; and (h) confirming that the test agent of step (b) is a candidate beta catenin modulating agent by detecting a change in the beta catenin pathway in the presence or absence of the test agent.

Applicants submit that Murray et al. do not teach a method comprising at least steps (e) – (h). Therefore, the Murray et al. reference does not anticipate the present claims because it fails to teach each and every step of the claimed methods. Accordingly, Applicants respectfully request withdrawal of the rejections under 35 USC § 102 (b).

Rejection of Claims Under 35 U.S.C. § 103

Claims 1-3, 6, 8-12, and 16-19 were rejected under 35 USC § 103(a) as allegedly being unpatentable over WO 03/052068 (Costa) as evidenced by Rennecke et al. (Eur. J. Biochem, 242:428-432 (1996) and Wetsel et al., (J Cell Biol, 117:121-133). Claims 12 and 16-19 have been canceled, rendering the rejection moot as to these claims. Applicants respectfully traverse the rejection with respect to claims 1-3, 6, and 8-11.

The Office alleged that the Costa et al. application teaches steps (a) – (c) of claim 1, except that it does not explicitly disclose a system comprising a PRKC nucleic acid. However, the Office stated that Costa et al. suggests using mammalian cell lines in the assay systems and that it is known in the art that mammalian cell lines comprise PRKC family genes. Further, the Office stated that the art shows that PRKC enzymes are ubiquitous in mammalian cells, as evidenced by Rennecke et al., which allegedly teaches that PKC mu is present in all cells and tissues and Wetsel et al., which allegedly teaches that PKC alpha is present in all tissues. Office Action, at pages 6-7. Thus, the Office concluded that it would have been obvious for one of ordinary skill in the art to use in the method of Costa et al. a cell line comprising at least one PKC nucleic acid. Office Action, at page 7.

Contrary to the Office's allegations, the teachings of Costa et al., Rennecke et al., and Wetsel et al., alone or in combination, do not render obvious the present invention.

The instant claims are directed to a method of identifying a candidate beta-catenin pathway modulating agent comprising the steps of: (a) providing a first assay system capable of detecting Protein Kinase C (PRKC) expression comprising a PRKC nucleic acid; (b) contacting the assay system of step (a) with a test agent; (c) measuring the expression of PRKC in the presence or absence of the test agent; (d) identifying a candidate beta catenin modulating agent by detecting a change in the expression or activity of PRKC in the presence of the test agent compared with no test agent; (e) providing a second assay system capable of detecting a change in the beta catenin pathway comprising cultured cells expressing PRKC; (f) contacting the assay system of step (e) with the candidate test agent of step (b); (g) measuring the beta catenin pathway in the presence or absence of the test agent; and (h) confirming that the test agent of step (b) is a candidate beta catenin modulating agent by detecting a change in the beta catenin pathway in the presence or absence of the test agent.

To meet the requirements for a *prima facie* case of obviousness, the Office must demonstrate that the references teach or suggest all the limitations of the claims. Post-KSR, the Board of Patent Appeals and Interferences (BPAI) has continued to maintain that:

[A]n examiner must make "a searching comparison of the claimed invention — *including all its limitations* - with the teaching of the prior art." *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis added). Thus, "obviousness requires a suggestion of all limitations in a claim." *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d, 1333, 1342 (Fed. Cir. 2003) (citing *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)). *Ex Parte Wada*, BPAI, Appeal 2007-377, page 7 (Jan. 15, 2008) (unpublished).

See also, Ex parte Shepard, BPAI, Appeal 2008-0401, page 7 (Jan. 3, 2008)(unpublished).

Applicants submit that Costa et al., Rennecke et al., and Wetsel et al., alone or in combination, fail to teach or suggest a method of identifying a candidate beta catenin pathway modulating agent comprising, *inter alia*, a first assay system comprising a PRKC nucleic acid, measuring the expression of PRKC in the presence or absence of a

test agent, identifying a candidate beta catenin modulating agent by detecting a change in the expression or activity of PRKC in the presence or absence of the test agent and then using a second assay system capable of detecting a change in the beta catenin pathway to confirm that the test agent is a beta catenin modulating agent.

The Office argued that it would have been obvious for one of ordinary skill in the art to use a cell comprising at least one PKC nucleic acid in the method of Costa et al. because it was known in the art that PKC is expressed ubiquitously in mammalian cells. However, even if a mammalian cell used in the claimed assay expresses PRKC, given that neither Costa et al, Rennecke et al., nor Wetsel et al. teaches the connection between PRKC and the beta catenin pathway, none of these references, alone or in combination, teaches or suggests the presently claimed assay in which the expression of PRKC is specifically measured in the presence or absence of a test agent and in which the candidate beta catenin modulating agent is identified by detecting a change in the expression or activity of PRKC in the presence or absence of the test agent. Moreover, none of the references teach or suggest using a second assay system capable of detecting changes in the beta catenin pathway to confirm that the test agent is a beta catenin pathway modulating agent.

Although the Costa et al. reference describes an assay for identifying a candidate beta catenin modulating agent, it fails to recognize the connection between PRKC and the beta catenin pathway. In fact, Costa et al. makes no mention whatsoever of PRKC and therefore fails to even contemplate a method of identifying a candidate beta catenin pathway modulating agent using an assay system that detects PRKC expression in the presence or absence of a test agent, much less teach or suggest the presently claimed methods. Neither Rennecke et al nor Wetsel et al. cure the deficiencies of Costa et al. Neither Rennecke et al. nor Wetsel et al. provides any teaching or suggestion whatsoever that PRKC is involved in modulating the beta-catenin pathway. Rennecke et al. merely describes the expression of PKC μ in various cell lines and tissues. Likewise, Wetsel et al. describes the expression of various isoforms of PRKC in various tissues. Thus, like Costa et al., neither Rennecke et al. nor Wetsel et al. recognizes a connection between PRKC and the beta-catenin pathway. Given that none of the cited references teach or

suggest a connection between PRKC and the beta catenin pathway, they fail to teach or suggest all of the limitations of the presently claimed methods, and thus fail to render the instant invention obvious.

Furthermore, one skilled in the art would not have been motivated to modify the method of Costa et al. to arrive at the presently claimed methods. Costa et al. is directed to a screening assay for identifying a beta-catenin pathway modulating agent. Through specific testing in a *c. elegans* system, the applicants in Costa et al. identified and named several nucleic acids involved in beta-catenin regulation: (1) RAG1AP1, (2) NOP16, (3) LOC87549, (4) DLG4, (5) DLG3, (6) DLG1, and (7) DLG2. Costa et al. did not identify any other genes involved in beta-catenin regulation; nor did the applicants suggest seeking further genes to be used in the assay. In fact, it is apparent from a reading of Costa et al. that all of the genes found to modulate beta-catenin were disclosed in Table I. Given that Costa et al. provides several genes that can be used in the assay to identify a beta-catenin modulating agent, one skilled in the art would not have been motivated to seek the use of alternative genes. Why would one prefer to seek and test yet another new nucleic acid, rather than simply use the nucleic acids that had already been shown to modulate beta-catenin and therefore determined to be useful in the described screening assays?

Moreover, Costa et al. make no mention whatsoever of the PRKC gene, much less contemplate or suggest using an assay comprising a PRKC nucleic acid or measuring the expression of PRKC expression in the described assay. Thus, even if, for the sake of argument, one skilled in the art would have been motivated to seek the use of a new, unidentified, untested nucleic acid rather than use a nucleic acid already determined to be useful in the described screening assay, given that Costa et al. provides no teaching whatsoever related to the PRKC gene, one skilled in the art would not have been motivated to specifically seek the use of a PRKC nucleic acid in an assay for identifying a candidate beta catenin modulating agent, much less seek the specific teachings of Rennecke et al and/or Wetsel et al.

Applicants respectfully submit that the Office has failed to establish a *prima facie* case of obviousness for the reasons set forth above. Accordingly, Applicant

respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejection based on Costa et al., Rennecke et al., and Wetsel et al.

Claims 1, 2, 6, and 8-10 were rejected under 35 USC § 103(a) as allegedly being unpatentable over Murray et al. (J. Biol. Chem. 268:15847-15853 (1993)) in view of Summerton et al., (Antisense & Nucleic Acid Drug Dev., 7: 187-195 (1997)). Applicants respectfully traverse the rejections.

The Office alleged that Murray et al. disclose a proliferation based assay wherein cells that express PKC α , β , and ζ were treated with antisense against PKC β . The Office stated that “the active method steps of the rejected claims provide absolutely no nexus between beta catenin, PRKC, and the candidate agents, such that these claims are anticipated by any prior art method in which an antisense oligonucleotide is added to cells in a proliferation assay, wherein the cells comprises PKC nucleic acids.” Office Action, page 7. The Office further alleged that Summerton et al. teach that phosphorodiamidate morpholino oligonucleotides overcome the problems associated with first generation antisense chemistries. The Office concluded that one of ordinary skill in the art would have been motivated to substitute PMO oligonucleotides for the standard oligonucleotide chemistry of Murray et al.

As discussed previously, to meet the requirements for a *prima facie* case of obviousness, the Office must demonstrate that the references teach or suggest all the limitations of the claims. Applicants submit that Murray et al. teaches the expression of PKC α , β , and ζ in human erythroleukemia cells and also teaches that PKC β antisense can decrease proliferation in these cells. Murray et al. makes no mention whatsoever of the beta catenin pathway, much less a connection between PKC and the beta catenin pathway. Summerton et al. is merely a review article directed to morpholino antisense oligomers, which fails to mention PKC or the beta catenin pathway.

In the absence of any teaching whatsoever of the beta catenin pathway or a connection between PKC and the beta catenin pathway, neither Murray et al., nor Summerton et al., alone or in combination, teach or suggest the claimed method of

identifying a candidate beta catenin modulating agent. In particular, the combined teachings fail to teach or suggest a method comprising the steps of, *inter alia*, (c) measuring the expression of PRKC in the presence or absence of the test agent; (d) identifying a candidate beta catenin modulating agent by detecting a change in the expression or activity of PRKC in the presence or absence of the test agent; (e) providing a second assay system capable of detecting a change in the beta catenin pathway comprising cultured cells expressing PRKC; (f) contacting the assay system of step (e) with the candidate test agent of step (b); (g) measuring the beta catenin pathway in the presence or absence of the test agent; and (h) confirming that the test agent of step (b) is a candidate beta catenin modulating agent by detecting a change in the beta catenin pathway in the presence or absence of the test agent.

Applicants respectfully submit that the Office has failed to establish a *prima facie* case of obviousness because the cited references, alone or in combination, fail to teach or suggest all of the limitations of the claimed methods. Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejection based on Murray et al. and Summerton et al.

Claims 1, 2, 6, 8, 9, 11, 12, 16, 18, and 19 were rejected under 35 USC § 103(a) as allegedly being unpatentable over Murray et al. (J. Cell Biol., 145: 699-711 (1999) ("Murray 1") in view of Murray et al. (J. Biol. Chem. 268:15847-15853 (1993)) ("Murray 2"). Claims 12 and 16, 18, and 19 have been canceled, rendering the rejection moot as to these claims. Applicants respectfully traverse the rejection with respect to claims 1, 2, 6, 8, 9, and 11.

The Office alleged that Murray 1 teaches that overexpression of PKC β induces colonic hyperproliferation and increases sensitivity to colon carcinogenesis in a transgenic mouse model. The Office further alleged that Murray 1 teaches that transgenic PKC β mice exhibit elevated colonic beta catenin, indicating that PKC β stimulates the Wnt/APC/beta catenin proliferative signaling pathway. The Office stated that Murray 1 does not teach the treatment of cells with antisense PCK β . The Office alleged that Murray 2 shows that antisense PCK β can inhibit the proliferation of PMA-withdrawn

cells, confirming the role of PKC β in cellular proliferation. The Office concluded that one of ordinary skill in the art would have been motivated to use the antisense of Murray 2 to treat the colonic cells of the mouse of Murray 1 in order to confirm that the activity of PKC β in those cells was responsible for the observed phenotype. The Office reasoned that, in so doing, one would have taken the PKC β antisense (allegedly anticipating claims 1, 2, 6, 8, and 9) and applied it in a second, animal-based model system in which the animal mis-expresses beta catenin, thereby rendering obvious the invention as a whole. Office Action, at page 9.

As discussed previously, to meet the requirements for a *prima facie* case of obviousness, the Office must demonstrate that the references teach or suggest all the limitations of the claims. Applicants submit that Murray 1 teaches the expression of PKC α , β , and ζ in human erythroleukemia cells and also teaches that PKC β antisense can decrease proliferation in these cells. Murray et al. makes no mention whatsoever of the beta catenin pathway, much less a connection between PKC and the beta catenin pathway. Murray 2 merely teaches a PKC β transgenic mouse that has elevated colonic beta catenin levels. Neither reference teaches or suggests a method for identifying a beta catenin pathway modulating agent by measuring the expression of PRKC in the presence or absence of a test agent. In particular, neither Murray 1 nor Murray 2, alone or in combination, teach or suggest the claimed method comprising the steps of, inter alia, (c) measuring the expression of PRKC in the presence or absence of the test agent; (d) identifying a candidate beta catenin modulating agent by detecting a change in the expression or activity of PRKC in the presence or absence of the test agent; (e) providing a second assay system capable of detecting a change in the beta catenin pathway comprising cultured cells expressing PRKC; (f) contacting the assay system of step (e) with the candidate test agent of step (b); (g) measuring the beta catenin pathway in the presence or absence of the test agent; and (h) confirming that the test agent of step (b) is a candidate beta catenin modulating agent by detecting a change in the beta catenin pathway in the presence or absence of the test agent.

Applicants respectfully submit that the Office has failed to establish a *prima facie* case of obviousness because the cited references, alone or in combination, fail to teach or

suggest all of the limitations of the claimed methods. Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejection based on Murray 1 and Murray 2.

Conclusion

In view of the foregoing amendments and remarks, the applicant submits that the claims are in condition for allowance, which is respectfully solicited. If the examiner believes a teleconference will advance prosecution, he is encouraged to contact the undersigned as indicated below.

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Respectfully submitted,

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